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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 20

Application Number	10/601,442
Filing Date	6/23/2003
First Named Inventor	Fensome et al.
Art Unit	1614
Examiner Name	D. Jones
Attorney Docket Number	AHPWA22AUSA

Certificate DEC 26 2006 of Correction

ENCLOSURES (Check all that apply)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation
- ☐ Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please identify below):
  Request for Certificate of Correction

Remarks

Customer No: 38199

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Howson & Howson		
Signature	Cathy A Kodroff		
Printed name	Cathy A. Kodroff		
Date	12-20-2006	Reg. No.	33,980

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	S Uchin		
Typed or printed name	Summer Uchin	Date	Dec 20, 2006

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 10/601,442	Confirmation No.: 7993
Applicant	: Fensome et al.	
Filed	: June 23, 2003	
Patent No.	: 7,115,649	
Issue Date	: October 3, 2006	
TC/Art Unit	: 1614	
Examiner	: D. Jones	
Customer No.	: 38199	
Title	: METHODS OF TREATING SKIN DISORDERS USING THIO-OXINDOLE DERIVATIVES	

Attention: Certificate of Corrections Branch
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 35 USC SECTION 254

Sir:

The following errors were found in the above-identified patent.

1. Col. 3, Line 47, replace "$NRC^{C}OR^{B}$;" with -- $NR^{C}COR^{B}$; --.
2. Col. 6, Line 61, replace "Nor" with -- N or --.

CERTIFICATE OF TRANSMISSION OR MAILING
UNDER 37 CFR 1.8

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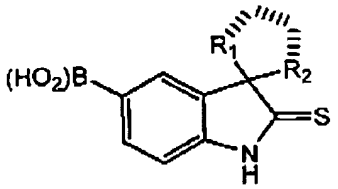
Signed _____
Printed Name Summer Uchin
Dated: Dec. 20, 2006

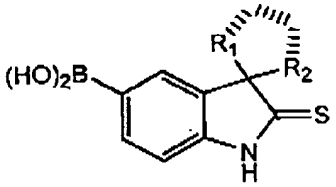
3. Col. 14, Line 2, replace "optiQnally" with -- optionally --.

4. Col. 18, Scheme 4, replace the following structure:



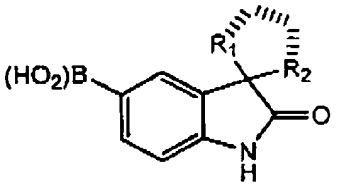
14

with the following structure:



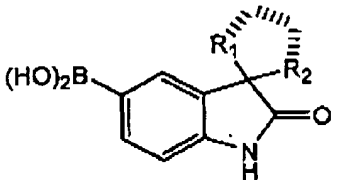
14

5. Col. 19, Scheme 5, replace the following structure:



14

with the following structure:



14

6. Col. 29, Line 16, replace "when'the" with -- when the --.

7. Col. 33, Line 29, replace "5-(5-Cyano-1-methyl-1H-pyrrol-2-yl)" with -- 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl) --.

8. Col. 41, Line 3, replace "X" with -- X^2 --.
9. Col. 44, Line 65, replace "beterocyclic" with -- heterocyclic --.
10. Col. 45, Line 24, replace "C_3" with -- C_6 --.
11. Col. 45, Line 50, replace "aryl, substituted C_1" with -- aryl, substituted aryl, C_1 --.
12. Col. 45, Line 57, replace "C_3 alkyl" with -- C_4 alkyl --.
13. Col. 46, Line 1, replace "c_1" with – C_1 --.
14. Col. 46, Line 14, replace "C_3" with -- C_6 --.
15. Col. 46, Line 15, replace ", substituted C_3 to C_6" with -- , substituted C_1 to C_6 --.
16. Col. 46, Line 50, replace "-$CH_2(CH_2)_2CH_2$-," with -- -$CH_2(CH_2)_nCH_2$-, --.
17. Col. 46, Line 64, replace "ospiro[cyclohekane-1,3-[3H]indol]-5'-yl)-2-" with -- ospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2- --.
18. Col. 47, Line 1, replace "[3H]-indol]-5'-yl)-2-" with -- [3H]-indol]-5-yl)-2- --.

It is requested that a Certificate of Correction be issued to correct the above errors in accordance with the enclosed forms, which are submitted herewith.

Because all errors were made by the US Patent and Trademark Office (USPTO), no fee is due for correction of these errors. To support Applicants' assertion that these are USPTO errors, Applicants have enclosed a copy of the original specification pages as filed which contain the correct language for errors (1) - (7) noted above. The correct language in these original specification pages is identified by a handwritten bolded box.

Errors (8) - (18) were also typographical errors in the claims on the part of the USPTO. To support this assertion, Applicants' have enclosed copies of the relevant pages of the Response filed on April 18, 2006 which contains the correct language for original claim 11, issued claim 12; original claim 23, issued claim 19; original claim 21; issued claim 21 and original claim 24, issued claim 23.

AHPWA22AUSA

The director of the US Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 08-3040.

Respectfully submitted,
HOWSON & HOWSON LLP
Attorneys for Applicant

By: Cathy A Kodroff

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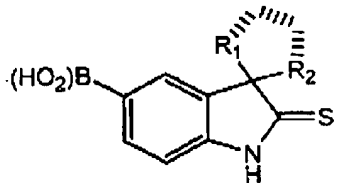
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	7,115,649
APPLICATION NO.	10/601,442
ISSUE DATE.	October 3, 2006
INVENTOR(S).	Fensome et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

1. Col. 3, Line 47, replace "NRC^COR^B;" with -- NR^CCOR^B; --.
2. Col. 6, Line 61, replace "X^1 is Nor CX^2;" with -- X^1 is N or CX^2; --.
3. Col. 14, Line 2, replace "optiQnally" with -- optionally --.
4. Col. 18, Scheme 4, replace the following structure:



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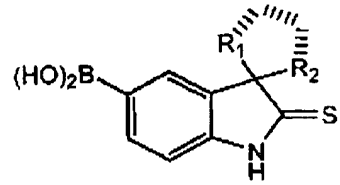
with the following structure:



14

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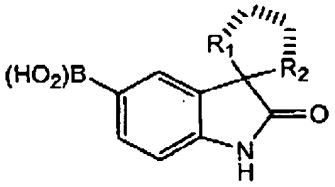
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	7,115,649
APPLICATION NO.	10/601,442
ISSUE DATE.	October 3, 2006
INVENTOR(S).	Fensome et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

5. Col. 19, Scheme 5, replace the following structure:



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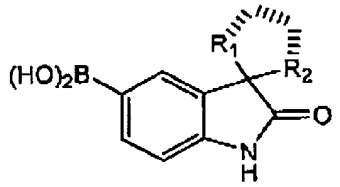
with the following structure:



14

6. Col. 29, Line 16, replace "when'the" with -- when the --.

7. Col. 33, Line 29, replace "5-(5-Cyano-1-methyl-1H-pyrrol-2-yl)" with -- 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl) --.

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CERTIFICATE OF CORRECTION

PATENT NO.	7,115,649
APPLICATION NO.	10/601,442
ISSUE DATE.	October 3, 2006
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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

8. Col. 41, Line 3, replace "X" with -- X^2 --.
9. Col. 44, Line 65, replace "beterocyclic" with -- heterocyclic --.
10. Col. 45, Line 24, replace "C_3" with -- C_6 --.
11. Col. 45, Line 50, replace "aryl, substituted C_1" with -- aryl, substituted aryl C_1 --.
12. Col. 45, Line 57, replace "C_3 alkyl" with -- C_4 alkyl --.
13. Col. 46, Line 1, replace "c_1" with -- C_1 --.
14. Col. 46, Line 14, replace "C_3" with -- C_6 --.
15. Col. 46, Line 15, replace ", substituted C_3 to C_6" with -- , substituted C_1 to C_6 --.
16. Col. 46, Line 50, replace "-$CH_2(CH_2)_2CH_2$-," with -- -$CH_2(CH_2)_nCH_2$-, --.
17. Col. 46, Line 64, replace "ospiro[cyclohekane-1,3-[3H]indol]-5'-yl)-2-" with -- ospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2- --.
18. Col. 47, Line 1, replace "[3H]-indol]-5'-yl)-2-" with -- [3H]-indol]-5-yl)-2- --.

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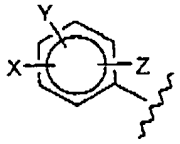
Fort Washington, PA 19034

R^5 is selected from the group consisting of a), b) and c):

a) a substituted benzene ring having the structure:



X is selected from the group consisting of halogen, OH, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, S(O)alkyl, $S(O)_2$alkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, substituted C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring comprising 1 to 3 heteroatoms, $CONH_2$, $CSNH_2$, CNHNHOH, CNH_2NOH, CNHNOH, COR^B, CSR^B, $OCOR^B$, and NR^CCOR^B;

R^B is selected from the group consisting of H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, and substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independently selected from the group consisting of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 thioalkyl, and substituted C_1 to C_3 thioalkyl;

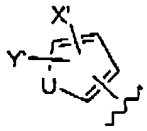
b) a five or six membered heterocyclic ring comprising 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 and having one or two independent substituents from the group consisting of H, halogen, CN, NO_2, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, COR^D, CSR^D, and NR^ECOR^D;

R^D is H, NH_2, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y is selected from the group consisting of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, and C_1 to C_3 thioalkyl;

(ii) a five membered ring having the structure:



wherein:

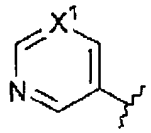
U is O, S, or NR^6;

R^6 is H, C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl;

X' is selected from the group consisting of halogen, CN, NO_2, $CONH_2$, CNHNHOH, CNH_2NOH, $CSNH_2$, CONHalkyl, CSNHalkyl, $CON(alkyl)_2$, $CSN(alkyl)_2$, C_1 to C_3 alkyl, and C_1 to C_3 alkoxy;

Y' is selected from the group consisting of H, F, and C_1 to C_4 alkyl; or

(iii) a six membered ring having the structure:



wherein:

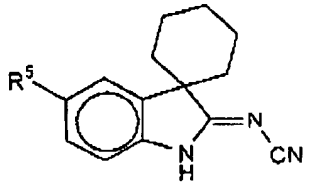
X^1 is N or CX^2;

X^2 is halogen, CN, $CONH_2$, $CSNH_2$, CONHalkyl, CSNHalkyl, $CON(alkyl)_2$, $CSN(alkyl)_2$ or NO_2;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

Preferably, R^5 is the five membered ring (ii) and U is O or S.

In yet another embodiment, the compound is of formula III:



III

point of attachment is through the oxygen-atom and the aryl group is optionally substituted.

The term "alkylcarbonyl" as used herein refers to the C(O)(alkyl) group, where the point of attachment is through the carbon-atom of the carbonyl moiety and the alkyl group is optionally substituted.

The term "alkylcarboxy" as used herein refers to the C(O)O(alkyl) group, where the point of attachment is through the carbon-atom of the carboxy moiety and the alkyl group is optionally substituted.

The term "aminoalkyl" as used herein refers to both secondary and tertiary amines where the point of attachment is through the nitrogen-atom and the alkyl groups are optionally substituted. The alkyl groups can be the same or different.

The term "halogen" as used herein refers to Cl, Br, F, or I groups.

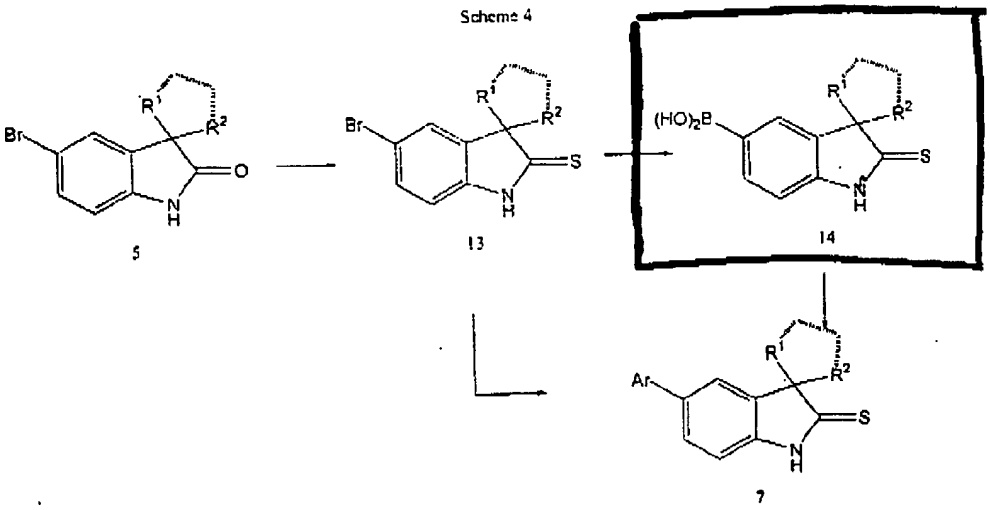
The compounds of the present invention encompass tautomeric forms of the structures provided herein characterized by the bioactivity of the drawn structures. Further, the compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids, bases, alkali metals and alkaline earth metals.

Physiologically acceptable acids include those derived from inorganic and organic acids. A number of inorganic acids are known in the art and include hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, and phosphoric acids, among others. Similarly, a variety of organic acids are known in the art and include, without limitation, formic, acetic, propionic, oxalic, succinic, glycolic, glucuronic, maleic, furoic, fumaric, citric, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, panthenoic, benzenesulfonic, stearic, sulfanilic, alginic, and galacturonic acids, among others.

Physiologically acceptable bases include those derived from inorganic and organic bases. A number of inorganic bases are known in the art and include aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc sulfate or phosphate compounds, among others. A number of organic bases are known in the art

Reaction of the indoline-2-one derivative 6 with either Lawessen's reagent or phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent provides access to the thiocarbonyl derivative 7. An additive such as sodium hydrogen carbonate can also be useful.

Scheme 4

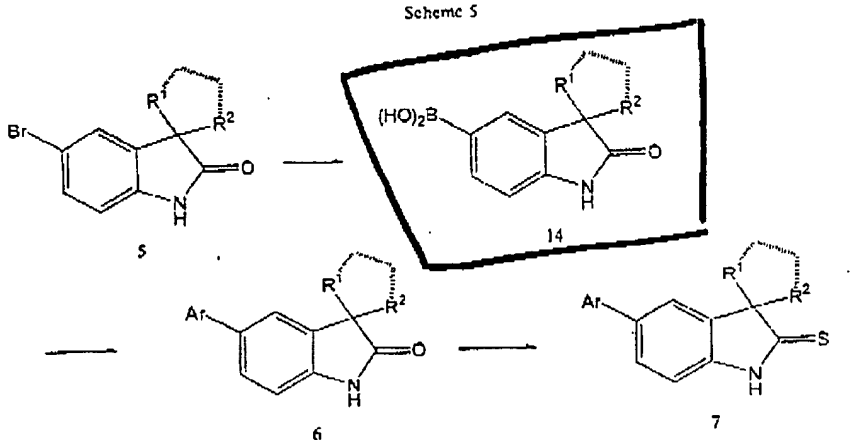


An alternative mode of preparation is to react compound 5 with either Lawessen's reagent or phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent, under an inert atmosphere (nitrogen or argon) providing access to the thiocarbonyl derivative 13. The reaction of bromide 13 in an anhydrous solvent (e.g. THF, Et_2O) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and N,N,N,N'-tetramethylethylenediamine followed after a suitable period of time by a trialkylborate (trimethyl or triisopropylborate) gives after acidic work-up the boronic acid 14 (Scheme 4). Compound 14 can then be reacted under palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0) or palladium acetate, base ($NaHCO_3$,

Na_2CO_3, K_2CO_3, triethylamine, CsF) solvent (toluene/EtOH/water, THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, to provide the desired compounds 7.

Alternatively reaction of compound 13 under palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0) or palladium acetate, base ($NaHCO_3$, Na_2CO_3, K_2CO_3, triethylamine, CsF) solvent (acetone/water, toluene/EtOH/water, THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, to provide the desired compound 7.

Scheme 5



Treatment of the bromide 5 in an anhydrous solvent (e.g. THF, Et_2O) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and N,N,N,N'-tetramethylethylenediamine followed after a suitable period of time by a trialkylborate (trimethyl or triisopropylborate) gives after acidic work-up the boronic acid 15 (Scheme 5). Compound 15 can then be reacted under palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0), base ($NaHCO_3$, Na_2CO_3, K_2CO_3, triethylamine, CsF) solvent (toluene/EtOH/water,

European Patent No. 314,206, among others); hydrophobic membrane materials, such as ethylenemethacrylate (EMA) and ethylenevinylacetate (EVA); bioresorbable polymer systems (International Patent Publication No. WO 98/44964 and US Patent Nos. 5,756,127 and 5,854,388); and other bioresorbable implant devices composed of, for example, polyesters, polyanhydrides, or lactic acid/glycolic acid copolymers (US Patent No. 5,817,343). For use in such sustained delivery devices, the compounds of the invention can be formulated as described herein. See, US Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719.

In yet another embodiment, the compounds are topically delivered using a topical vehicle including creams, pastes, gels, ointments, lotions, liquids, solutions, suspensions, or foams or can be alone delivered prior or subsequent to the topical vehicle. Topical compositions can be applied to the area of the body which is afflicted with the skin disorder and includes the face, scalp, legs, arms, torso, or armpits. Preferably, the topical vehicles are anti-comedogenic.

Skin conditioning agents can include any reagent which provides a conditioning effect to the skin and/or does not clog the pores of the skin. A number of skin conditioning agents are known in the art and include, without limitation, skin conditioning agents that can be applied to the skin, including water-based lotions, creams, pastes, gels, ointments or foams.

The regimens of the invention can include the continuous delivery of the compounds of the invention. In another embodiment, the regimens can include the periodic discontinuation of delivery of the compounds of the invention. Such periodic discontinuation can include delivery of a placebo during the period of time where the compounds of the invention are not delivered to the patient. Alternatively, no placebo or active agent is delivered to the patient when the compounds are not being delivered to the patient.

By the term "placebo" or "inactive agent" is meant a reagent having pharmacological properties that are not relevant to the condition being treated, i.e.,

dose units of an estrogen; and, optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0 to 9 days in the 28-day cycle.

In a preferred embodiment, a 28-day kit can include a first phase of 21 daily dosage units of a compound of formula I; a second phase of 3 daily dosage units for days 22 to 24 of an estrogen; and, optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Preferably, the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is delivered. It is further preferable that the daily dose units described are to be delivered in the order described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle.

A number of packages or kits are known in the art for the use in dispensing pharmaceutical agents for oral use. Preferably, the package has indicators for each day of the 28-day cycle, and more preferably is a labeled blister package, dial dispenser package, or bottle.

The following examples are provided to illustrate the invention and do not limit the scope thereof. One skilled in the art will appreciate that although specific reagents and conditions are outlined in the following examples, modifications can be made which are meant to be encompassed by the spirit and scope of the invention.

EXAMPLES

Example 1 – Treatment of Acne

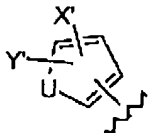
A twenty-five year old human patient having acne vulgaris is treated according to the present invention. Specifically, 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide is orally delivered to the patient daily. Delivery is in the form of a tablet formulated to contain about 20 mg of

wherein:

X is selected from the group consisting of halogen, CN, $CONH_2$, $CSNH_2$, CONHalkyl, CSNHalkyl, $CON(alkyl)_2$, $CSN(alkyl)_2$, CNHNHOH, CNH_2NOH, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring comprising 1 to 3 heteroatoms, and C_1 to C_3 thioalkyl;

Y is selected from the group consisting of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, and C_1 to C_3 thioalkyl;

(ii) a five membered ring having the structure:



wherein:

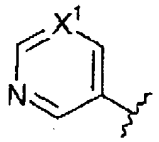
U is O, S, or NR^6;

R^6 is H, C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl;

X' is selected from the group consisting of halogen, CN, NO_2, $CONH_2$, CNHNHOH, CNH_2NOH, $CSNH_2$, CONHalkyl, CSNHalkyl, $CON(alkyl)_2$, $CSN(alkyl)_2$, C_1 to C_3 alkyl, and C_1 to C_3 alkoxy;

Y' is selected from the group consisting of H, F, and C_1 to C_4 alkyl; or

(iii) a six membered ring having the structure:



wherein:

X^1 is N or CX^2;

X^2 is halogen, CN, $CONH_2$, $CSNH_2$, CONHalkyl, CSNHalkyl, $CON(alkyl)_2$, $CSN(alkyl)_2$ or NO_2;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

X^2 is halogen, CN, $CONH_2$, $CSNH_2$, CONHalkyl, CSNHalkyl, $CON(alkyl)_2$, $CSN(alkyl)_2$ or NO_2;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

18-19(Canceled).

20(Previously Presented). The method according to claim 22, wherein:

R^1 and R^2 are alkyl or substituted alkyl;

R^3 is H.

21(Previously Presented). The method according to claim 22, wherein:

R^1 and R^2 are joined to form a ring selected from the group consisting of $-CH_2(CH_2)_nCH_2-$, $-CH_2CH_2C(CH_3)_2CH_2CH_2-$, $-O(CH_2)_mCH_2-$, $-O(CH_2)_pO-$, $-CH_2CH_2OCH_2CH_2-$, $-CH_2CH_2N(H)CH_2CH_2-$, and $-CH_2CH_2N(alkyl)CH_2CH_2-$;

R^3 is H.

22(Previously Presented). The method according to claim 22, wherein:

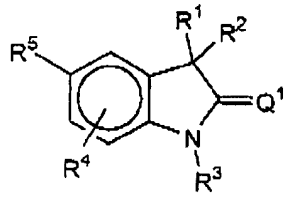
R^3 is H;

Q^1 is S or NR^7.

23(Previously Presented). A method of conditioning the skin comprising the step of delivering to a mammal in need thereof a composition comprising:

(i) a skin conditioning component; and

(ii) a compound of formula I, or a tautomer thereof:



I

wherein:

R^1 and R^2 are selected from the group consisting of H, alkyl, substituted alkyl, OH, O(alkyl), O(substituted alkyl), O(Acetyl), aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, alkylaryl, substituted alkylaryl, alkylheteroaryl, substituted alkylheteroaryl, 1-propynyl, substituted 1-propynyl, 3-propynyl, and substituted 3-propynyl;

or R^1 and R^2 are joined to form a ring selected from the group consisting of $-CH_2(CH_2)_nCH_2-$, $-CH_2CH_2C(CH_3)_2CH_2CH_2-$, $-O(CH_2)_mCH_2-$, $-O(CH_2)_pO-$, $-CH_2CH_2OCH_2CH_2-$, $-CH_2CH_2N(H)CH_2CH_2-$, and $-CH_2CH_2N(alkyl)CH_2CH_2-$;

m is an integer from 1 to 4;

n is an integer from 1 to 5;

p is an integer from 1 to 4;

or R^1 and R^2 form a double bond to $C(CH_3)_2$, C(cycloalkyl), O, or C(cycloether);

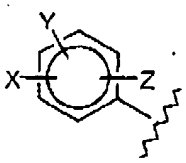
R^3 is selected from the group consisting of H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, and COR^A;

R^A is selected from the group consisting of H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, and substituted C_1 to C_3 aminoalkyl;

R^4 is selected from the group consisting of H, halogen, CN, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, and substituted C_1 to C_6 aminoalkyl;

R^5 is selected from the group consisting of a), b) and c):

a) a substituted benzene ring having the structure:



X is selected from the group consisting of halogen, OH, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3

thioalkyl, substituted C_1 to C_3 thioalkyl, S(O)alkyl, $S(O)_2$alkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, substituted C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring comprising 1 to 3 heteroatoms, $CONH_2$, $CSNH_2$, CNHNHOH, CNH_2NOH, CNHNOH, COR^B, CSR^B, $OCOR^B$, and NR^CCOR^B;

R^B is selected from the group consisting of H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, and substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independently selected from the group consisting of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 thioalkyl, and substituted C_1 to C_3 thioalkyl;

b) a five or six membered heterocyclic ring comprising 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 and having one or two independent substituents from the group consisting of H, halogen, CN, NO_2, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, COR^D, CSR^D, and NR^ECOR^D;

R^D is H, NH_2, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^6 is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or C_1 to C_4CO_2alkyl; or

c) an indol-4-yl, indol-7-yl or benzo-2-thiophene moiety, wherein said moiety is optionally substituted by from 1 to 3 substituents selected from the group consisting of halogen, alkyl, substituted alkyl, CN, NO_2, alkoxy, substituted alkoxy, and CF_3;

Q^1 is S, NR^7, or CR^8R^9;

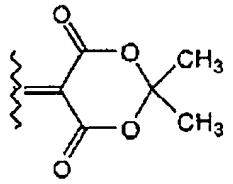
R^7 is selected from the group consisting of CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl,

heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, SO_2CF_3, OR^{11}, and $NR^{11}R^{12}$;

R^8 and R^9 are independent substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, NO_2, CN, and CO_2R^{10};

R^{10} is C_1 to C_3 alkyl or substituted C_1 to C_3 alkyl;

or CR^8R^9 comprise a six membered ring having the structure:



R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, sulfonyl, and substituted sulfonyl;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

24(Previously Presented). The method according to claim 23 wherein said compound of formula I is selected from the group consisting of 5'-(3-Chlorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-thione, 3-(1',2'-Dihydro-2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)benzonitrile, 4-1',2'-Dihydro-2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2-thiophenecarbonitrile, 3-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-5-fluorobenzonitrile, 4-Methyl-5-(1,2-dihydro-2-thioxospiro[cyclohexane-1,3-[3H]-indol]-5-yl)-2-thiophenethioamide, 5-(1,2-Dihydro-2-thioxospiro[cyclopentane-1,3-[3H]indol]-5'-yl)-1H-pyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1-(tert-butoxycarbonyl)-pyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1-H-pyrrole-2-carbonitrile, 5-(2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1-methyl-pyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-